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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/914,508 | 11/07/2001 | Becrelli Seshi | 0152.00418 | 8090 |

23557 7590 10/10/2003

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

| EXAMINER | |
|---|---|
| AFREMOVA, VERA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1651 | |

DATE MAILED: 10/10/2003 12

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/914,508 | SESHI, BEERELLI | |
| | Examiner | Art Unit | |
| | Vera Afremova | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *42-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *42-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/2/2003* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of claims*

New claims 42-62 are pending and under examination in the instant office action. Paper No. 10 filed 7/28/2003.

Applicant cancels claims 1-41. Paper No. 10 filed 7/28/2003.

### *Claim Rejections - 35 USC § 112*

### *New matter*

Claims 50-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "**each**" of said cells simultaneously expresses a plurality of genes that are markers for multiple cell lineages comprising at least four different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cell has no support in the as-filed specification.

Insertion of the limitation "**at least 95%** of said plurality of cells is **a cell**" that simultaneously expresses a plurality of genes that are markers for multiple cell lineages comprising at least 4 different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cell has no support in the as-filed specification.

The insertions of these limitations is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the

newly limited genus which would show possession of the concept that "**each**" cell or "**at least 95%** of said cells simultaneously expresses a plurality of genes that are markers for multiple cell lineages comprising at least four different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cell has no support in the as-filed specification.

For example: the as-filed specification does not provide a literal support for the concept of **"each"** cell meaning the possession of a 100% homogenous cell population. Further, with respect to the exemplified disclosure, it appears that neither 100% nor at least 95% of cells are homogenous with regard to the simultaneous expression of a plurality of genes that are markers for 4 different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cell. For example: only 85% of cells are disclosed as being characterized by expressions of the fourth cell lineage marker such as muscle cell marker actin (see page 14, line 29 or see table on page 29). The amount of "greater than 85%" as disclosed is not a sufficient support for the new genus of "each" or "at least 95%". This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of limitations "**each**" and "**at least 95%**" is considered to be the insertion of new matter for the above reasons.

***Indefinite***

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 is indefinite because it is uncertain what is a meaning of the term "isolated" in the context of this particular claim. It is uncertain from what the cells are "isolated" in the cell composition as claimed. It is uncertain whether the cells are an "isolated" cell line or clone. It is uncertain whether each cell is "isolated" by encapsulation, for example. In the instant office action the term "isolated" cell(s) is interpreted as cell(s) derived and/or separated from an original source such as bone marrow, for example. However, the claim 56 does not appear to indicate an intention to point out a source of origin or a source of isolation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42-62 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,879,940.

Claims are directed to an isolated pluri-differentiated mesenchymal progenitor cell (MPC) that simultaneously expresses a plurality of genes that are markers for multiple cell lineages. Some claims are further drawn to the cell lineages comprising at least four different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cell. Some claims are further drawn to the expression of specific markers of four lineages including Oil Red O (adipocyte), alkaline phosphatase (osteoblast), fibronectin (fibroblast) and actin (muscle cell). Some claims are further drawn to the expression of plurality of genes in the presence of hydrocortisone and horse serum. Some claims are further drawn to the cell being not neoplastic. Some claims are/are further drawn to a composition with MPC(s) and a pharmaceutical carrier.

Some claims are further drawn to the composition with MPC(s) in amount effective for treating a disease state in a mammal, to enhance hematopoietic stem cell engraftment or to treat graft-versus-host disease (GvHD). Some claims are further drawn to a plurality of MPC(S) wherein at least 95% of cells simultaneously express genes that are markers for adipocyte, osteoblast, fibroblast and muscle cells.

US 5,879,940 discloses isolated stromal cell(s) derived from bone marrow (col. 13, table 1) that are pluri-differentiated mesenchymal progenitor cell(s) within the meaning of the claimed invention and according to the applicant's definitions (page 12, lines 4-7). The cells of the cited patent belong to the mesenchymal cell lineage and they simultaneously expresses a plurality of genes that are markers for at least four different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cell including adipocyte marker such as Oil Red O (col. 14, lines 30), osteoblast marker such as alkaline phosphatase, fibroblast marker such as fibronectin and muscle cell marker such as actin (table 1). The cells were obtained and cultured under the same conditions such as in the presence of hydrocortisone and horse serum (col. 11, lines 45-50). Thus, the mesenchymal cell(s) of the cited patent are characterized by the same phenotype as the presently claimed "pluri-differentiated" cell(s). The cells of the cited patent are progenitor cells because they are capable for further differentiation, for example: they are disclosed as "pre-adipocytic" (col. 15, line 1) and they accumulate lipid vacuoles in the presence of a differentiation promoting agent dexamethasone (col. 14, line 47). The cells of the cited patent are considered to be the mesenchymal progenitor cells within the meaning of the claimed invention because they expresses genes of at least four different mesenchymal cell lineages as required for the claimed "pluri-differentiated mesenchymal progenitor" cell(s). Although the cells of the cited

patent are immortalized and have some increased growth rates, they are considered to be "not neoplastic" within the meaning of the claims because they retain the characteristics of normal bone marrow derived cells after immortalization (col. 14, line 54). The instant specification does not provide definitions as to what is considered to be "not neoplastic" cell in the applicant's invention. The cells of the cited patent are not tumorogenic as disclosed. Moreover, they are disclosed as being capable to supporting short and long term hematopoiesis (example 2) and, thus, they are reasonably considered to be therapeutically effective and, therefore, non tumorogenic or "not neoplastic". The cited patent teaches a composition with MPC(s) and a carrier such as serum-deprived medium, for example: col. 15, line 64. The compositions are considered to comprise MPC(s) in amounts effective for treating a disease state in a mammal, to enhance hematopoietic stem cell engraftment or to treat graft-versus-host disease (GvHD) in a patient about undergo bone marrow transplantation because the cells of the cited patent are taught and have been demonstrated as being effective in supporting hematopoiesis. The cells of the cited patent are the cells of the same type or one-type cells as disclosed and, thus, they are pure or at least 95% pure as required for the claimed plurality of isolated cells.

Therefore, the cited patent US 5,879,940 teaches cells and cell compositions identical to the presently claimed cell(s) and cell compositions.

Claim rejections under 35 U.S.C. 102 as being anticipated by Pittenger et al. [U] in the light of teaching by Ager et al. [X] or as being anticipated by US 6,010,696 [A] have been withdrawn because Pittenger et al. and US 6,010,696 disclose the mesenchymal stem cell(s) that express the cell lineage specific markers under different differentiation conditions and, thus, they

can not be said to simultaneously expresses a plurality of genes that are markers for multiple cell lineages including at least four different mesenchymal cell lineages such as adipocyte, osteoblast, fibroblast and muscle cells as argued by applicants (pages 10-11, response filed 7/28/2003).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Majumdar et al. taken with US 5,879,940 and Bordignon et al. {[IDS reference R5 which is [V] as indicated in the last office action}.

Claims as explained above.

The reference by Majumdar et al. teaches a marrow derived stromal cell population "MDSC(s)" which is cultured in the presence of hydrocortisone and horse serum (see page 58, paragraph-bridging columns 1 and 2). The reference is silent with regard to the expression of markers of 4 different cell lineages by the cell population MDSC(s).

However, the cited patent US 5,879,940 demonstrates that the mesenchymal progenitor cells of the same cell population derived from bone marrow and cultured in the presence of hydrocortisone and horse serum as the MDSC(s) of Majumdar et al. are capable to simultaneously express markers of 4 different cell lineages including adipocyte, osteoblast, fibroblast and muscle cells.

The cited reference by Majumdar et al. teaches that MDSC(s) support hematopoiesis (page 65, col. 1). But it is silent with regard to effective amounts intended for treating a disease state in a mammal, to enhance hematopoietic stem cell engraftment in a mammal or to treat graft-versus-host disease (GvHD).

However the reference by Bordignon et al. teaches clinical applications of cultured stromal cells for treating various disease state in mammals (page 1138, col. 1, par. 2) including modulation of graft-versus-host-disease (GvHD), autologous and allogeneic replacement of damaged tissues and enhancement of hematopoietic progenitor cell engraftment or transplantation (table 4, page 1138). The cultured stromal cells of the reference by Bordignon et al. include mesenchymal stem cells and mesenchymal progenitor cells that are committed to at least 4 cell lineages including adipocyte, osteoblast, fibroblast and muscle cell (page 1137, fig.7).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to obtain therapeutic compositions comprising effective amounts of mesenchymal progenitor pluri-differentiated cells with a reasonable expectation of success in treating various disease states in mammals including treating GvHD and/or enhancing hematopoietic progenitor cell engraftment or tissue transplantation because cultured marrow derived mesenchymal cells have been known and taught in the prior art as clinically suitable and therapeutically effective for treating various disease state in mammals including treating GvHD and/or enhancing hematopoietic progenitor cell engraftment or tissue transplantation. It is considered to be within the purview of one of ordinary skill in the art to adjust effective amounts of cells in the therapeutic cellular compositions depending on a particular protocol of clinical

treatment and/or severity of disease state or patient condition. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Although the cited reference by Majumdar et al. appears to recognize the MDSC(s) as a mixed cell population, the MDSC(s) disclosed by Majumdar et al. are reasonably expected to express the same markers as the immortalized mesenchymal progenitor cells of US 5,879,940 since they have been derived from identical source (bone marrow) and cultured/treated under the same conditions (in the presence of hydrocortisone and horse serum). Thus, the claimed cell(s) and composition with cell(s) would have been obvious to those skilled in the art within the meaning of USC 103 over the MDSC(s) disclosed by Majumdar et al.

Accordingly, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

***Response to Arguments***

Applicant's arguments with respect to new claims have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651

October 8, 2003

V.A

SANDRA E. SAUCIER
PRIMARY EXAMINER